Target Specific Oral Anticoagulants (TSOACs)
Dabigatran (Pradaxa), Rivaroxaban (Xarelto), Apixaban (Eliquis)
Criteria for Use for *Treatment of Venous Thromboembolism (VTE)*
February 2015
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. ***THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE OUTSIDE THE RECOMMENDATIONS SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.***

The Product Information should be consulted for detailed prescribing information. The VA National PBM-MAP-VPE TSOAC Class Review, individual Drug Monographs and CFU for Stroke Prevention in Atrial Fibrillation (AF) and VTE prophylaxis are available at www.pbm.va.gov or https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx.

Note for patients who are stable on warfarin therapy: Stable patients on warfarin may be effectively maintained on warfarin rather than switching to a TSOAC. Internal national VA metrics from August 2014 show 71% of patients receiving warfarin through the VA have an INR between 1.8 and 3.3.

Pivotal Acute VTE Study Summary:

	DABIGATRAN		RIVAROXABAN		APIXABAN
Pivotal study **TSOAC vs. warfarin/vitamin K antagonist (INR 2-3)**	RE-COVER Double-blind	RE-COVER II Double-blind	EINSTEIN DVT Open-label	EINSTEIN PE Open-label	AMPLIFY Double-blind
Mean age	55 yrs	55 yrs	56 yrs	58 yrs	57 yrs
Mean Time in Therapeutic Range (TTR)	60%	57%	58%	63%	61%
Efficacy: Recurrence of symptomatic VTE	Non-inferior	Non-inferior	Non-inferior	Non-inferior	Non-inferior
Safety: Major bleeding	Non-inferior	Non-inferior	Non-inferior	Superior	Superior
Safety: Major + nonmajor clinically relevant bleeding	Superior	Superior	Non-inferior	Non-inferior	Superior

No head to head studies of TSOACs are available; differences in trial design and patient populations limit the ability to make indirect comparisons between TSOACs.

EXCLUSION CRITERIA (if ONE is checked, patient is not eligible)

- ❑ Need for an anticoagulant for an indication other than VTE (DVT and/or PE) treatment or non-valvular AF (e.g., heart valve replacement)
- ❑ Prosthetic heart valve (See Issues for Consideration)
- ❑ Active endocarditis
- ❑ Active pathological bleeding
- ❑ Severe renal impairment[a]
  - Dabigatran: creatinine clearance (CrCl) <30 ml/min
  - Rivaroxaban: CrCl <30 ml/min
  - Apixaban: CrCl <25 ml/min or serum creatinine (SCr) >2.5 mg/dL
- ❑ Known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis, liver function test [LFT] elevations >2-3x upper limit of normal, Child-Pugh B or C or any hepatic disease associated with coagulopathy)
- ❑ For dabigatran, concurrent use of a significant P-glycoprotein (P-gp) interacting drug (See Comparative Table)
- ❑ For rivaroxaban and apixaban, concurrent use of a significant dual P-gp and CYP3A4 interacting drug (see Comparative Table)
- ❑ Previous hypersensitivity reaction to a TSOAC
- ❑ Pregnancy (i.e., known pregnancy or positive pregnancy test)
- ❑ Breastfeeding (See Issues for Consideration)
- ❑ Increased bleeding risk: medical condition or history of major bleed that would be considered a contraindication to anticoagulation (See Issues for Consideration)
- ❑ Patients with VTE in the setting of active cancer who are willing and able candidates for LMWH (see Issues for Consideration)

INCLUSION CRITERIA (ALL must be selected for patient to be eligible)

- ❑ Patient with objectively confirmed VTE (DVT and/or PE)
- ❑ Renal function assessment (CrCl) (see Monitoring for additional information)

For women of childbearing potential:

- ❑ Determine pregnancy status prior to starting TSOAC and provide contraceptive counseling. Discuss potential risk vs. benefit of TSOAC treatment during pregnancy. Women taking a TSOAC should notify their provider if they become pregnant.

DOSAGE AND ADMINISTRATION

- **VTE (DVT and/or PE) Treatment:**
  - Dabigatran: After 5 to 10 days of injectable anticoagulant, 150 mg twice daily
  - Rivaroxaban: 15 mg twice daily *with a full meal* for the first 21 days, then 20 mg once daily *with a full meal*
    Note: Rivaroxaban exhibits dose-dependent bioavailability. Higher doses, such as those used for VTE treatment, should be taken with a full meal to enhance absorption.
  - Apixaban: 10 mg orally twice daily for the first 7 days, then 5 mg orally twice daily.
- **Reduction of VTE recurrence** (after VTE treatment period):

- Dabigatran: 150 mg twice daily
- Rivaroxaban: 20 mg once daily *with a full meal*
- Apixaban: After at least 6 months of treatment, apixaban 2.5 mg twice daily (Note: reduced dose of apixaban was studied only in patients with clinical equipoise for continuing anticoagulation. Patients evaluated were mainly those with an unprovoked VTE. Patients with clear indications for continued anticoagulation treatment were not studied on the reduced dose.)

- See prescribing information for reduced dosing in special populations
- Due to lack of clinical data, PBM recommends avoiding the use of each TSOAC in the following degrees of renal impairment:
  - Dabigatran: CrCl <30 ml/min
  - Rivaroxaban: CrCl <30 ml/min
  - Apixaban: CrCl <25 ml/min or SCr >2.5 mg/dL

MONITORING

- **Patients should be monitored for adherence, signs and symptoms of bleeding, thromboembolic events, and other adverse effects.**
- Prior to starting TSOAC therapy, it should be assured that the patient does not have anemia or thrombocytopenia and has adequate and stable renal function. If patient has significant anemia or thrombocytopenia, the risk vs. benefit of full dose anticoagulation should be assessed prior to starting therapy. In patients with chronic kidney disease where CrCl may fluctuate or in patients >75 yrs of age, monitoring of serum creatinine should be performed more frequently at the discretion of the provider; therapy should be adjusted as needed.
- No routine laboratory monitoring of anticoagulant activity is recommended. Although changes in anticoagulation markers have been reported, the clinical significance is unclear.

ISSUES FOR CONSIDERATION

- **Spinal/Epidural Hematoma:** Like other anticoagulants, TSOAC labeling includes a boxed warning on the risk of spinal/epidural hematoma when the drug is used in patients receiving neuraxial (e.g., epidural or spinal) anesthesia or undergoing spinal puncture. Permanent paralysis may result. See package label for additional information.
- **Prosthetic heart valves:** Dabigatran, an oral direct thrombin inhibitor, is associated with an increased risk of adverse outcomes (e.g., valve thrombosis, stroke, myocardial infarction, bleeding) in patients with mechanical prosthetic heart valves. Patients with mechanical prosthetic heart valves were excluded from the pivotal AF trials. Because of the known adverse outcomes with a related agent (dabigatran) and the lack of data with rivaroxaban and apixaban, the TSOACs should not be used in patients with mechanical prosthetic heart valves. Regardless of indication, use of TSOACs in the setting of other forms of valvular disease, including the presence of a bioprosthetic valve, has not been specifically studied and is not recommended.
- **Contraindications due to increased bleeding risk:** Risk and benefit assessment for individual patients should be conducted. Some of the following examples may be considered relative contraindications depending on the patient scenario: anemia (hemoglobin <10 g/dL) or thrombocytopenia (platelet count <100,000/uL), cancer considered to be at risk for bleeding based on the type of cancer and/or type of cancer treatment being administered, history of intracranial, intraocular, spinal, retroperitoneal, atraumatic intra-articular bleeding, or gastrointestinal bleeding, uncontrolled hypertension (persistently elevated systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg), recent and concomitant treatment with fibrinolytic agent (refer to prescribing information [PI]), or chronic treatment with a nonsteroidal anti-inflammatory drug (NSAID).
- **Use in Significant Liver Disease:** see PI for details. Language in the product label and from the exclusion criteria of the pivotal trials differ between agents. Overall, avoid TSOAC use in patients with moderate-to-severe impairment - e.g., acute clinical hepatitis, cirrhosis, liver enzyme elevations (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]) >2-3x upper limit of normal), or hepatic disease associated with coagulopathy.
- **Pharmacodynamic Interactions:** Concomitant use of TSOACs and medications that affect hemostasis are expected to increase the risk of bleeding (aspirin, anti-platelet agents, other anticoagulants, fibrinolytics, nonsteroidal anti-inflammatory drugs (NSAIDs). Low dose aspirin (≤165 mg/day) combined with TSOACs (or warfarin) increases the risk of bleeding. In acute coronary syndrome (ACS) populations, the addition of apixaban (full dose), rivaroxaban (low dose), or dabigatran (varying dose) to aspirin plus a $P2Y_{12}$-receptor antagonist (e.g., clopidogrel) was found to significantly increase bleeding risk. The need for concurrent use of anti-platelet medications or other medications that may increase the risk of bleeding should be re-evaluated when a TSOAC is prescribed.
- **Reversal of anticoagulant effects:** There is no reversal agent for the TSOACs, although the drugs have a relatively short duration of action compared to warfarin. Information on the optimal management of bleeding with TSOACs is lacking. Management should be individualized according to the specific situation but may reasonably include discontinuation of treatment and implementation of supportive measures (compression, surgical hemostasis, transfusion). Dialysis may be effective for dabigatran but is not expected to be effective for removal of apixaban or rivaroxaban (given the high protein binding of the drugs). Activated charcoal may reduce absorption of the TSOACs and may be considered in cases of suspected overdose or bleeding if administered within 2 hours of the last TSOAC dose.
- **Switching from or to warfarin:** When switching from warfarin to a TSOAC, prescribing information recommends starting TSOAC when INR is < 3 (for rivaroxaban) and < 2 (for dabigatran and apixaban). TSOACs reach therapeutic effects within a few hours. When converting from TSOAC to warfarin, consider that TSOACs affect INR. If continuous anticoagulation is needed, discontinue TSOAC and start an injectable anticoagulant with warfarin at the time the next scheduled TSOAC dose would have been due. (See "Discontinuation of therapy" or Boxed Warning in prescribing information on the increased risk of thrombotic events)
- **Switching from or to anticoagulants other than warfarin:** Discontinue the anticoagulant being used and start the other at the next scheduled dose.
- **Interruptions in therapy for surgery and interventions:** If possible, TSOACs should be discontinued at least 24 hours prior to surgery or invasive procedures with an increased bleeding risk. Discontinuations of longer durations are recommended for surgery and procedures with a higher bleeding risk where complete hemostasis is required and for patients with renal impairment. Recommendations regarding alterations in anticoagulant therapy for dental procedures can be found at the American Dental Association at: http://www.ada.org/2526.aspx. The risk of thromboembolism off anticoagulation and the risk of peri-procedural bleeding need to be considered (See PIs and Comparative Table for

additional, more specific information).

- **Advanced age:** The risk of thrombotic and bleeding events increases with age. In the pivotal VTE treatment trials, the mean age was in the 50s and the portion of patients over 75 years ranged from 10% to 17% of the study population. Based on the available information from subgroup analysis, efficacy and safety of the TSOACs in the subgroup of elderly patients appear to be maintained. Consider the benefit along with the increased bleeding risk in patients of advanced age.
- **VTE in the setting of active cancer:** Patients with cancer are at higher risk for thromboembolism (and death following VTE) and may be at higher risk of bleeding as part of their underlying cancer or chemotherapy. Low molecular weight heparin (LMWH) has been shown to be superior to vitamin K antagonists (VKA) for the reduction in the risk of VTE in patients with cancer and is preferred in professional guidelines (In the CLOT trial, symptomatic, recurrent VTE probability at 6 months: 17% with warfarin vs. 9% with LMWH). Studies of the TSOACs for VTE treatment included only small numbers of patients with cancer (range of 3-6%) and compared TSOAC to VKA, a known inferior therapy in this population. Subgroup analyses have been performed but are of limited value given the small number of patients and events. Until there are additional data on the efficacy and safety of TSOACs in patients with VTE and active cancer, alternative treatments (e.g., LMWH) should continue to be preferred in this population. Patients with active cancer who are not candidates for LMWH may be considered for warfarin or a TSOAC. The TSOAC trials included very limited numbers of these patients with active cancer, and thus specific recommendations cannot be made based on the evidence.
- **Known thrombophilia:** Patients with a known thrombophilia (e.g. antiphospholipid antibody syndrome) comprised a small part of the pivotal VTE study populations (range of 2-8%), thus the treatment effect of TSOACs in these patients is unclear.
- **Recurrent VTE:** In the pivotal acute VTE studies with the TSOACs, the portion of patients with a history of prior VTE ranged between 15% and 26% of the study population. The treatment effect of the TSOACs in this subgrouphas not been definitively established.
- **Extended treatment:** Patients were treated for the acute episode for 3, 6, or 12 months in the pivotal clinical trials. The decision to extend VTE treatment is based on individual consideration of recurrent VTE risk and bleeding. Periodic reassessment of risk-benefit should be performed. Long-term data (e.g., beyond about a year) is lacking.
- **Breastfeeding:** It is not known whether the TSOACs are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse events in nursing infants from a TSOAC, a decision should be made to discontinue breastfeeding or discontinue the TSOAC.
- **Pregnancy:** PBM recommends generally avoiding the TSOACs during pregnancy because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible.
- **Coronary Artery Disease:** Dabigatran was associated with a small but consistently elevated risk of myocardial infarction (MI)/acute coronary syndrome (ACS) in clinical trials. Overall, there appears to be about a 30% relative increase in MI/ACS that translates to about a 0.2-0.3% annual absolute increase in events with dabigatran. No excess of MI/ACS with rivaroxaban or apixaban has been observed.
- **Altered gastrointestinal absorption:** There are no clinical data evaluating the TSOACs in patients with prior bariatric surgery, gastric bypass, or other procedures or conditions where gastrointestinal absorption could be significantly altered.
- **Extremes of Body Weight:** Pharmacokinetic studies of apixaban demonstrate increased drug exposure for patients weighing ≤50 kg and reduced drug exposure for patients weighing >120 kg. Rivaroxaban pharmacokinetic studies did not find that body weight influenced drug exposure. Pivotal clinical studies for VTE treatment did not identify significant differences in treatment effect or safety in subgroup analysis of patients with low or high body weight for rivaroxaban, apixaban, or dabigatran. No dosage adjustments are recommended by the manufacturers; however, caution should be used when prescribing TSOACs to patients with extremes of body weight.
- **Fall Risk:** Consider occupation with predisposition to falls (i.e. construction, athletes, those working in remote locales with limited transport), functional status (those with prosthetics, or who are wheelchair or bedbound), ability to perform activities of daily living, prior falls, dementia, frailty, as well as post-operative consequences on functional status before initiation given irreversible nature of the TSOACs and the risk for higher morbidity and mortality in acute trauma.
- **Adherence to drug regimen:** Patients should be able to adhere to a twice daily drug regimen with dabigatran and apixaban and to a once daily regimen with rivaroxaban. Adherence rates were very high with the TSOACs in the pivotal clinical trials, and it is unclear how outcomes may be affected with lower adherence rates, given their relatively short half-lives.
- **Dual care patients:** All patients receiving the drug from VA should be managed according to the same standards (e.g., eligibility, monitoring, follow-up), consistent with the VHA National Dual Care Directive 2009-038.

[a]In the pivotal trials evaluating TSOACs for VTE treatment, CrCl was estimated using the Cockcroft-Gault equation. Dabigatran is primarily eliminated by the kidneys. Rivaroxaban is less dependent and apixaban is minimally dependent on renal elimination compared to dabigatran. For patients with a CrCl of 30-50 ml/min, providers may reasonably prefer to use an alternative to dabigatran, particularly if the patient's renal function may fluctuate.

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Anticoagulation Algorithm – Considerations for Selection of Target-Specific Oral Anticoagulants (TSOACs) for Venous Thromboembolism (VTE) Treatment in VA Patients

Patient with Acute VTE

Target Specific Oral Anticoagulant (TSOAC) or warfarin (WARF)?

- WARF and TSOACs are acceptable 1st line agents
- WARF may be effectively initiated or continued in the setting of good INR control and acceptability to patient and provider
- TSOACs generally not recommended and WARF should be used in patients with the following:
  - CrCl <30 ml/min or end stage renal disease (ESRD) on dialysis
  - Prosthetic heart valve (regardless of indication)
  - Additional indication for anticoagulation other than DVT/PE or nonvalvular atrial fibrillation history
  - On concomitant therapy with interacting drugs
- TSOACs are not recommended as first line treatment of VTE in patients with active cancer in the absence of sufficient efficacy and safety data. Low molecular weight heparin (LMWH) has been shown to be superior to WARF and remains the preferred anticoagulant in this population.
- TSOACs may be useful in the setting of poor INR control on WARF despite adherence, difficulty obtaining regular INR checks, and drug interactions that can't be managed by adjusting WARF dose

Decision to use TSOAC has been made
(Consider all clinical factors prior to final drug selection)

Is patient at increased risk of bleed*?

YES

Consider APIX
- Bleeding rates similar-to-lower with TSOACs vs. WARF
- APIX was associated with less bleeding vs. WARF
- More GI bleeding with DABI vs. WARF

NO

Does the patient have renal impairment? (CrCl† ≤50 ml/min)

YES

Consider RIVA or APIX
- Portion of renal elimination of TSOACs: DABI > RIVA > APIX
- APIX undergoes minor renal elimination
- RIVA undergoes significant renal elimination
- DABI primarily undergoes renal elimination; DABI OK if no drug interactions are present and patient is not at high bleed risk* (DABI should be avoided if on a P-gp inhibitor and CrCl ≤50 ml/min)

NO

Consider DABI or other TSOAC

* Examples of factors that increase bleeding risk include advanced age, renal impairment, history of bleeding, concomitant use of meds that affect bleeding, hypertension, prior stroke, and anemia. Several bleeding risk score systems that were developed for warfarin (e.g., HAS_BLED, Outpatient Bleeding Risk Index, HEMORR$_2$HAGES) are available, though their predictability has been shown to be limited.

† CrCl was estimated using the Cockcroft-Gault equation in the pivotal clinical trials of TSOACs (and using actual body weight in the dabigatran and rivaroxaban trials).

Notes:

- ❑ **All three TSOACs are reasonable for the treatment of acute VTE. Choice of specific agent should be based on clinical considerations and local policy.**
- ❑ **The algorithm is not all inclusive, and complex patients may not fit the algorithm. Clinical judgment should be used.**
- ❑ No head to head studies between TSOACs have been conducted; considerations for one agent over another are based on data from pivotal trials with a TSOAC vs. warfarin or on indirect comparisons of TSOACs.
- ❑ See comparative table for more information
- ❑ Patients with CAD: DABI is associated with a small but significant increased risk of MI when data are considered in total. It is not known whether patients with CAD are at higher risk of events with DABI. Triple therapy (ASA, P2Y$_{12}$ antagonist and anticoagulant) is associated with increased bleeding vs. dual antiplatelet therapy
- ❑ RIVA and APIX are initiated without the need for initial therapy with an injectable anticoagulant.
- ❑ RIVA is the only once daily TSOAC

APIX=apixaban; CAD=coronary artery disease; CrCl=creatinine clearance; DABI= dabigatran; DVT=deep vein thrombosis; GIB= gastrointestinal bleed; INR=international normalized ratio; PE=pulmonary embolism; RIVA= rivaroxaban; WARF=warfarin; VTE=venous thromboembolism

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Updated versions can be found at www.pbm.va.gov or https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx

COMPARATIVE TABLE: CONSIDERATIONS IN CHOICE OF ORAL ANTICOAGULANT FOR *VTE TREATMENT*

	DABIGATRAN	RIVAROXABAN	APIXABAN	WARFARIN
Dosing	150 mg BID *after 5-10 days of injectable anticoagulant*	15 mg BID for 21 days, then 20 mg once daily	10 mg BID for 7 days, then 5 mg BID After at least 6 mos tx, reduce dose to 2.5 mg BID	Variable dose; once daily
Special considerations	Caps cannot be crushed or opened Caps must be stored in original container	Cannot be administered via feeding tube placed distal to stomach Can be crushed	Can be crushed	Can be crushed
Dietary considerations	Take with full glass of water	Must take with meal for adequate absorption	None	Steady intake of Vitamin K containing foods
Renal impairment *Note: The VA PBM recommendations for renal dosing are based on evidence from the pivotal clinical trials and may differ from information provided in the package label.*	Primarily renal elimination	Significant renal elimination	Minor renal elimination	Minimal renal elimination
	PBM recommendations: Avoid if CrCl <30 ml/min (not studied) **Avoid if CrCl <50 ml/min and on concomitant P-gp inhibitors**	**PBM recommendations: Avoid if CrCl <30 ml/min (not studied)**	**PBM recommendations: Avoid if SCr >2.5 mg/dL or CrCl <25 ml/min (not studied)**	n/a
	Package Labeling: No dosing recommendations if CrCl <30 ml/min Avoid use if CrCl <50 ml/min and on concomitant P-gp inhibitors	Package Labeling: Avoid if CrCl <30 ml/min	Package Labeling: No adjustments	n/a
Prosthetic Heart Valve	Data showing increased adverse outcomes in mechanical prosthetic valves; contraindicated; not recommended for other valvular disease	Not studied and not recommended	Not studied and not recommended	Standard of care for oral anticoagulation
Geriatric Patients	No increased bleed risk vs. warfarin identified There are no data on safety and efficacy of using a reduced dose of 75 mg BID empirically in elderly	No increased bleed risk vs. warfarin identified	No increase bleed risk vs. warfarin identified Reduced dose not studied	Consider lower initiation dose and greater sensitivity to dose/INR response in elderly
PUD/GI issues	GIB more frequent vs. warfarin Increased GI adverse effects (e.g., dyspepsia, gastritis) vs. warfarin	No info	No increased GIB vs. warfarin	Less GIB vs. DABI
Additional indications for anticoagulation	FDA approved for: ▪ stroke prevention in nonvalvular AF	FDA approved for: ▪ Stroke prevention in nonvalvular AF ▪ VTE prophylaxis in orthopedic surgery	FDA approved for: ▪ Stroke prevention in nonvalvular AF ▪ VTE prophylaxis in orthopedic surgery	Several indications for use
CAD considerations	Numerical increase in MI vs. warfarin in VTE treatment and AF trials	None	None	None
ASA/thienopyridine concomitant use	Increased bleeding Little data on ASA+thienopyridine in AF; Increased bleed with unknown benefit in Phase 2 study of ACS pts	Increased bleeding No data on ASA+thienopyridine in AF; Increased bleed with benefit in ACS pts (low dose rivaroxaban)	Increased bleeding No data on ASA+thienopyridine in AF; Increased bleed without benefit in ACS pts	Increased bleeding
(Cont'd)	**DABIGATRAN**	**RIVAROXABAN**	**APIXABAN**	**WARFARIN**
Drug interactions	Prodrug is substrate of P-	CYP3A4, P-gp substrate	CYP3A4, P-gp substrate	Alterations in plasma

	gp AVOID use P-gp inducers (e.g., rifampin, St. John's Wort)- reduced dabigatran effect AVOID use with P-gp inhibitors (e.g., dronedarone, ketoconazole) and concurrent renal impairment (CrCl <50 ml/min)	AVOID use with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin) – reduced rivaroxaban effect AVOID use with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir and ritonavir combinations)- increased rivaroxaban effect	AVOID use with strong P-gp and CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin) – reduced apixaban effect Reduced dose of apixaban 2.5 mg BID available for use with strong P-gp and CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, and ritonavir combinations) – increased apixaban effect	protein binding; CYP2C9, 1A2, 3A4 induction or inhibition; antibiotics, antifungals, herbals
Switching from WARF	Start TSOAC when INR <2	Start TSOAC when INR <3	Start TSOAC when INR <2	n/a
Switching to WARF	DABI affects INR	RIVA affects INR	APIX affects INR	n/a
Surgery and Invasive Procedures *The risk of thromboembolic events vs. peri-op bleeding should be considered with use of anticoagulant therapy; expert consultation may be warranted.*	(From PI) Discontinue 1-2 days (if CrCl ≥50 ml/min) or 3-5 days (CrCl <50 ml/min) before invasive procedures or surgery. Consider longer times for higher risk procedures where complete hemostasis is required.	(From PI) Discontinue at least 24 hrs before surgery or procedures with increased bleeding risk.	(From PI) Discontinue at least 24 hrs prior to surgery/procedures where risk of bleeding is low and could be easily managed. Discontinue at least 48 hrs prior to surgery/procedures with moderate to high bleeding risk.	Depending on risks of bleeding with the procedure and thromboembolic events off of anticoagulation, warfarin may be held and bridge therapy with injectable anticoagulant considered.
Anticoagulant Lab testing	None routinely recommended; if urgently needed, aPTT, TT (qualitative estimate; presence or absence)	None routinely recommended; if urgently needed, PT, anti-Factor Xa (qualitative estimate; presence or absence)	None routinely recommended; if urgently needed, anti-Factor Xa (qualitative estimate; presence or absence)	INR
Anticoagulant Reversal	No reversal agent; discontinue drug, provide supportive care. Hemodialysis may be effective.	No reversal agent; discontinue drug, provide supportive care.	No reversal agent; discontinue drug, provide supportive care.	Vitamin K, fresh frozen plasma (FFP), 4-factor prothrombin complex concentrate (PCC) for life threatening bleeding